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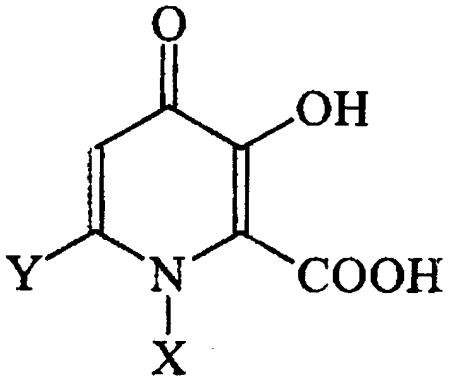
(54) Title: CARBOXYLIC ACID DERIVATIVES OF 3-HYDROXY-4-OXO-1,4-DIHYDROPYRIDINE AS IRON CHELATORS

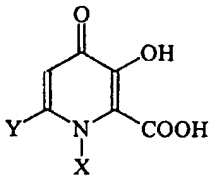


Formula I

(57) Abrégé/Abstract:
A novel 3-hydroxy-4-oxo-1,4-dihydropyridines of formula 1 and its pharmaceutically salt: (see formula I) in which X and Y are defined in the description. The compounds are effective as chelators of iron. They are useful in therapy, particularly in the treatment of conditions in which there is a toxic concentration of iron in the body.

ABSTRACT

A novel 3-hydroxy-4-oxo-1,4-dihydropyridines of formula I and its pharmaceutically salt:



Formula I

in which X and Y are defined in the description. The compounds are effective as chelators of iron. They are useful in therapy, particularly in the treatment of conditions in which there is a toxic concentration of iron in the body.

CARBOXYLIC ACID DERIVATIVES OF 3-HYDROXY-4-OXO-1,4-DIHYDROPYRIDINE AS IRON CHELATORS

The present invention relates to the field of iron chelators.

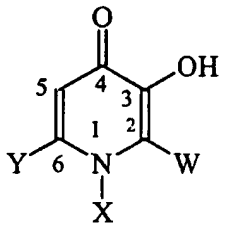
Background of the Invention

Mammals sparingly excrete iron and the iron is conserved within the body. Regular blood transfusion of patients suffering from certain disease such as beta-thalassemia will lead to elevated body iron levels because human cannot excrete iron via the kidney. Iron chelator drugs are used to complex excess tissue Fe(III) and transform it into an excretable form. There are two known iron chelator drugs Desferrioxamine B (Desferral) and Ferriprox (Deferriprone). Desferral has a short biological half-live and cannot be administered orally. Ferriprox (Deferriprone) is an orally active iron chelator drug, but is rapidly inactivated by phase II metabolism. High oral dose is required because of the extensive biotransformation. Therefore, there is a need for an orally active iron chelator with improved biological profile.

Summary of Invention

The present invention provides a group of 3-hydroxy-4-oxo-1,4-dihydropyridine derivatives of formula I, commonly known as 3-hydroxy-4-pyridone, with a carboxylic acid (COOH group) attached to the C2 position of the 1,4-dihydropyridine ring. A large number of 1-alkyl-3-hydroxy-4-oxo-1,4-dihydropyridine derivatives (also known as 1-alkyl-3-hydroxy-pyridin-4-one derivatives) are known in the literature, none of them has a carboxy group attached to the C2-position of the 1,4-dihydropyridine ring (Figure 1). The synthesis and biological activities of 1-alkyl-2-carboxy-3-hydroxy-4-oxo-1,4-dihydropyridine derivatives are unknown in the literature. The only known 3-hydroxy-1,4-dihydropyridine-2-carboxylic acids are 1,4-dihydro-3-hydroxy-4-oxo-2,6-pyridinedicarboxylic acid (JP2001199869, Chemical Abstract 135:126940), 1,4-dihydro-3-hydroxy-4-oxo-picolinic acid, 1-(p-carboxyphenyl)-1,4-dihydro-3-hydroxy-4-oxo-2,6-dicarboxylic acid ethyl ester (Mertes et. al., J. Heterocycl. Chem. (1969), 6(6), 941-3). These compounds differ from the

compound of this invention in that they do not have an alkyl or cycloalkyl group at the N-position of the 3-hydroxy-4-oxo-1,4-dihydropyridine ring.



= Ligand = L

Figure 1

In order to chelate iron, the 3-hydroxy-4-oxo-1,4-dihydropyridine chelator of Figure 1 (ligand = L) extracts iron (III) to form an 1 : 3 iron complex FeL_3 at physiological pH. In the absence of a carboxy group at the C2 position of the 3-hydroxy-4-oxo-1,4-dihydropyridine ring, the FeL_3 complex behaves like a neutral organometallic molecule. Most of them are soluble in dichloromethane and behaves as non-polar organic compounds on thin layer chromatography (TLC) and silica gel column chromatography. Figure 2 shows a normal FeL_3 complex:

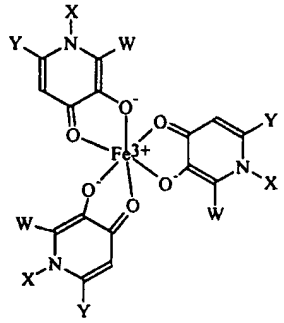


Figure 2

The substituent W is not a carboxy group. In this invention, therapeutically useful of 3-hydroxy-4-oxo-1,4-dihydropyridine iron chelators are designed to

complex excess tissue Fe(III) and transform it into a soluble and excretable form. An orally active chelator is more efficacious when the FeL_3 is soluble and easily excretable. The use of a carboxy group as a substituent on the C2 position of 3-hydroxy-4-oxo-1,4-dihydropyridine ring serves that function because the resulting 1 : 3 iron complex is a trisodium salt FeL_3Na_3. An example of FeL_3Na_3 complex is shown in Figure 3 below.

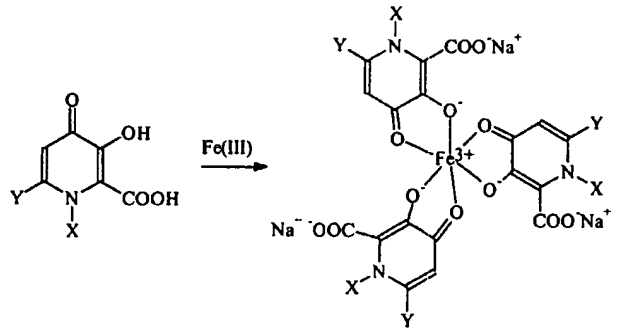


Figure 3

The sodium carboxylate salt facilities the excretion of the 1 : 3 iron-chelator complex. The use of carboxylic acid functionality in iron chelator ICL-670A to effect $Fe(ICL\text{-}670A)_2Na_3$ complex has been reported in the literature (Rouan et. al., J. of Chromatography B, 775 (2001), 203-213).

Figure 4 shows the structure of $Fe(ICL\text{-}670A)_2Na_3$ complex.

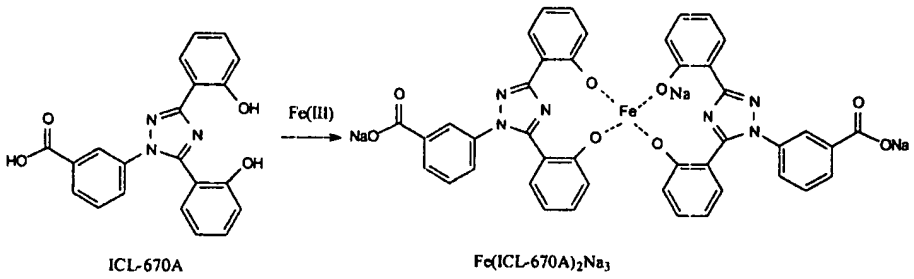


Figure 4

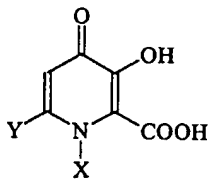
ICL-670A differs from the compound of this invention in that ICL-670A is a high molecular weight compound and is not a 3-hydroxy-4-oxo-1,4-

dihydropyridine. Compounds of this invention are low molecular weight compounds.

US patents 6,335,353, 6,177,409, 5,688,815, 4,840,958 described hydroxypyridones as iron chelators for the removal of excess iron in the bodies of animals. These iron chelators do not have a COOH group at the C2 position of the 3-hydroxy-4-oxo-1,4-dihydropyridine ring. Therefore they are incapable of forming a soluble sodium carboxylate salt when the iron complex chelate FeL_3 is formed. Compounds of this invention are 3-hydroxy-4-oxo-1,4-dihydropyridine that contains a COOH group at the C2 position of the are 3-hydroxy-4-oxo-1,4-dihydropyridine ring. The resulting iron complex formed is of the formula FeL_3Na_3. This novel approach in using the COOH group at the C2 position of the 3-hydroxy-4-oxo-1,4-dihydropyridine allows the iron chelator complex to be excreted as a soluble form FeL_3Na_3. Iron chelator drug is dosed every day to thalassemia major patients and therefore we must take into consideration the effectiveness of excreting the formed iron chelate in a soluble form to avoid the accumulation of the iron chelate and its reabsorption in the body.

The compounds used in the present invention are characterized by a 3-hydroxy-4-oxo-1,4-dihydropyridine ring structure, substituted at position 2 with a carboxylic acid, but unsubstituted at position 5.

The invention relates to novel 3-hydroxy-4-oxo-1,4-dihydropyridines represented by formula I:



Formula I

wherein:

X is C_1-C_6 alkyl, C_3-C_6 cycloalkyl, and a C_1-C_6 alkyl substituted by a hydroxy group or a carboxylic acid ester, $CONH_2$, SO_2NH_2, sulfo acid ester, C_1-C_6 alkyoxy, benzyloxy or C_6-aryloxy ether thereof,

Y is hydrogen, C_1-C_6 alkyl, CH_2OR', $CH_2NR'R''$, CO-NHR' wherein R', R" are independently C_1-C_6 alkyl,
or a pharmaceutically acceptable salt of such compound.

In a second aspect, this invention relates to a pharmaceutical composition comprising a compound of formula I and at least one pharmaceutically acceptable excipient.

In a third aspect, this invention concerns methods of using compounds of formula I, or a pharmaceutically acceptable salt thereof, as iron chelators to complex iron to form an iron chelate.

In a fourth aspect, this invention concerns synthetic process for the preparation of compounds of formula I.

An additional element of this invention involves a method in using an effective amount of compound of formula I as a ligand L to remove iron via the formation of a water soluble iron complex chelate FeL_3Na_3.

One preferred class of compound of formula I is a compound of formula I wherein:

X is C_1-C_6 lower alkyl,
Y is C_1-C_6 lower alkyl.

The most preferred class of compound is a compound of formula I wherein:

X is C_1-C_6 lower alkyl,
Y is hydrogen, methyl.

Compounds of formula I can form iron complex chelate with Fe(III) in solution. The information can be found in example 3 below.

The compounds of this invention are named as 3-hydroxy-4-oxo-1,4-dihydropyridine using the numbering system set forth in Figure 1.

The compound of formula I in which X is methyl, Y is methyl, is named 3-hydroxy-1,6-dimethyl-4-oxo-1,4-dihydropyridine-2-carboxylic acid.

As used herein:

"Alkyl" means a branched or unbranched saturated hydrocarbon chain having, unless otherwise noted, one to six carbon atoms, including but not limited to methyl, ethyl, propyl, isopropyl, n-propyl, butyl, sec-butyl, isobutyl, n-pentyl, hexyl, and the like.

Cycloalkyl refers to a cyclic hydrocarbon radical consisting solely of carbon and hydrogen, containing no unsaturation and having from three to eight carbon atoms, e.g. cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl.

C_1-C_6 alkyl substituted by a hydroxy group refers to a hydroxy group attached to the C_1-C_6 alkyl chain, e.g. $-CH_2CH_2OH$, $-CH(OH)CH_2$, $-CH_2CH_2CH_2OH$.

A carboxylic acid ester refers to a group COOR wherein R is C_1-C_6 alkyl. C_1-C_6 alkyl substituted by COOR group refers to the attachment of COOR to the C_1-C_6 alkyl, e.g. $-CH_2CH_2COOCH_3$, $-CH_2-CH(COOEt)-CH_3$.

C_1-C_6 alkyl substituted by a $CONH_2$ group refers to a $CONH_2$ group attached to the C_1-C_6 alkyl chain, e.g. $-CH_2CONH_2$, $-CH_2CH_2CONH_2$.

C_1-C_6 alkyl substituted by a SO_2NH_2 group refers to a SO_2NH_2 group attached to the C_1-C_6 alkyl chain, e.g. $-CH_2\ SO_2NH_2$, $-CH_2CH_2\ SO_2NH_2$.

A sulfo acid ester refers to SO_2OR wherein R is C_1-C_4 alkyl. C_1-C_6 alkyl substituted by SO_2OR group refers to the attachment of SO_2OR to the C_1-C_6 alkyl, e.g. $-CH_2CH_2\ SO_2OCH_3$, $-CH_2-CH(SO_2OCH_2CH_3)-CH_3$.

C_1-C_6 alkyl substituted by a C_1-C_6 alkyoxy group refers to a C_1-C_6 alkyoxy group attached to the C_1-C_6 alkyl chain, e.g. $-CH_2OCH_3$, $-CH_2CH_2OCH_2CH_3$.

Benzyloxy refers to $Ph-CH_2-O-$. C_6-aryloxy refers to Ph-O-.

C_1-C_6 alkyl substituted by a benzyloxy ether group refers to a benzyloxy group attached to the C_1-C_6 alkyl chain, e.g. $-CH_2CH_2OCH_2Ph$, $-CH_2CH_2CH_2OCH_2Ph$.

C_1-C_6 alkyl substituted by a C_6 aryloxy ether group refers to a phenoxy group attached to the C_1-C_6 alkyl chain, e.g. $-CH_2CH_2OPh$, $-CH_2CH_2CH_2OPh$.

"Pharmaceutically acceptable non-toxic salts" refers to pharmaceutically acceptable salts of the compounds of this invention, which retain the biological activity of the parent compounds and are not biologically or otherwise undesirable (e.g. the salts are stable). Salts of the two types may be formed from the compounds of this invention: (1) Salts of inorganic and organic bases from compounds of formula I which has a carboxylic acid functional group, and (2) Acid addition salts may be formed at the amine functional group from compounds of formula I of this invention.

Pharmaceutically acceptable salts derived from inorganic bases include sodium, potassium, lithium, ammonium, calcium, magnesium, ferrous, zinc, copper, manganous, aluminum, ferric, manganic salts and the like. Particularly preferred are the ammonium, potassium, sodium, calcium and magnesium salts. Pharmaceutically acceptable non-toxic salts derived from organic bases include salts of primary, secondary and tertiary amines,

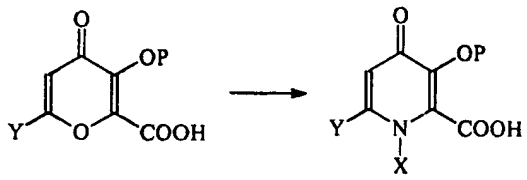
substituted amines including naturally occurring substituted amines, cyclic amines and basic ion exchange resins. Such salts are exemplified by, for example isopropopylamine, trimethyl-amine, diethylamine, triethylamine, tripropylamine, ethanolamine, 2-dimethylaminoethanol, tromethamine, dicyclohexamine, lysine, arginine, histidine, caffeine, procaine, hydrabramine, choline, betaine, ethylenediamine, glucosamine, methylglucamine, theobromine, purines, piperazine, piperidine, N-ethylpiperidine, polyamine resins and the like. Particularly preferred organic non-toxic bases are isopropylamine, diethylamine, ethanolamine, piperidine, tromethamine, dicyclohexylamine, choline and caffeine.

Pharmaceutically acceptable acid addition salts are formed with inorganic acids such as halo acids, sulfuric acid, nitric acid, phosphoric acid and the like and organic acids such as acetic acid, propionic acid, glycolic acid, pyruvic acid, oxalic acid, malic acid, malonic acid, succinic acid, maleic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid, salicylic acid and the like.

Preparation of compound of formula I:

Compound of formula I is prepared according to the procedure shown in Scheme 1.

Scheme 1:

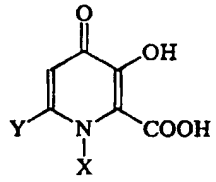


II III

A compound of formula II wherein P is an alcohol protective group, Y is as the same as defined above in the compound of formula I, is reacted an amine XNH_2, wherein X is C_1-C_6 alkyl, C_3-C_6 cycloalkyl, in an inert solvent such as dimethylformamide, methanol, ethanol or a mixture of these inert solvents at refluxing temperature of the solvent in a low pressure glass line reactor to give a compound of formula III wherein Y and P are as defined in compound II, and X is C_1-C_6 alkyl, C_3-C_6 cycloalkyl. The chemistry of alcohol protective group has been extensively described in Protective Groups in Organic Synthesis, 3rd edition, Editor: Theodora Greene & Peter G.M. Wuts, John Wiley & Sons 1999. Deprotection of the P group of compound III affords compound of formula I.

The preferred group for P is the benzyl group which can easily be removed by catalytic hydrogenation. Compound of formula III wherein P is benzyl is converted to a compound of formula I, by catalytic hydrogenation over 5 to 10% palladium on charcoal or 5 to 10% palladium hydroxide on charcoal in an inert alkanol such as methanol or ethanol. The compound is isolated by conventional means. Derivatives of formula II is known in the art, one example of this is the compound wherein P = benzyl, Y =methyl. The compound is known as 3-(benzyloxy)-6-methyl-4-oxo-4*H*-pyran-2-carboxylic acid (US application No. 09/985,269). Another example of a derivative of compound of formula II is 3-hydroxy-4-oxo-4H-pyran-2,6-dicarboxylic acid (S. Lovell et. al., J. Am. Chem. Soc. 1999, 121, 7020-7025) which can be converted to the O-benzyl derivative 3-benzyloxy-4-oxo-4H-pyran-2,6-dicarboxylic acid with sodium hydroxide and benzyl bromide in water.

Therefore, in this invention, we report a process for the preparation of compound of formula I:



Formula I

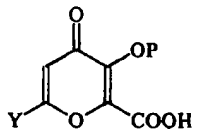
wherein:

X is C_1-C_6 alkyl, C_3-C_6 cycloalkyl,

Y is hydrogen, C_1-C_6 alkyl, CH_2OR', $CH_2NR'R''$, CO-NHR' wherein R', R" are independently hydrogen, C_1-C_6 alkyl;

which comprises of the following steps:

(a) Reacting a compound of formula II:

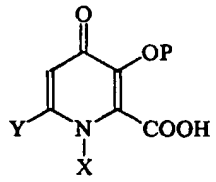


Formula II

wherein:

Y is hydrogen, C_1-C_6 alkyl, CH_2OR', $CH_2NR'R''$, CO-NHR' wherein R', R" are independently C_1-C_6 alkyl;

P is an alcohol protective group with an alkylamine XNH_2, wherein X is C_1-C_6 alkyl, C_3-C_6 cycloalkyl to give a compound of formula III:



Formula III

wherein:

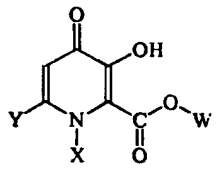
Y is hydrogen, C_1-C_6 alkyl, CH_2OR', $CH_2NR'R''$, CO-NHR' wherein R', R" are independently hydrogen, C_1-C_6 alkyl,

X is C_1-C_6 alkyl, C_3-C_6 cycloalkyl;

(b) Deprotecting the alcohol protective group P of a compound of a formula III from step (a) to give a compound of formula I.

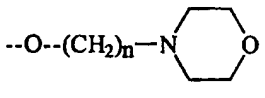
Compound of formula I wherein X is C_1-C_6 alkyl, C_3-C_6 cycloalkyl, are new chemical entities that are unknown in the literature. There are no methods known for the synthesis of such compounds. Although not specifically described, compound of formula I wherein X is a C_1-C_6 alkyl substituted by a hydroxy group or a carboxylic acid ester, $CONH_2$, SO_2NH_2, sulfo acid ester, C_1-C_6 alkyoxy, benzyloxy or C_6-aryloxy ether thereof, can also be prepared by the methods as described above.

The ester derivatives of compound of formula I, namely compound of formula IV:



Formula IV

wherein:

X and Y are defined the same as under the compound of formula I, and W is C_1-C_6 alkyl,  wherein n is 2 to 4,

can be prepared by standard procedure known in the literature. Vogel's Textbook of Organic Chemistry, by Hannaford, Smith and Tatchell, Longman Scientific and Technical (Fifth edition), details the various procedures for the preparation of an ester from a carboxylic acid on P.697 to 707.

Compounds of formula IV are prodrugs. These ester derivaties will undergo hydrolysis in the body to give the compounds of formula I. The concept of

ester prodrugs to mask the acid function of drug substances can be found in the following publications: Hudkins et.al. Bioorganic and Medicinal Chemistry Letters (United Kingdom), 1998, 8(14), 1873-1876; Tammara et. al., Pharmaceutical Research, 1993, 10(8):1191. Therefore, this disclosure also explains the use of ester derivatives of formula IV as prodrugs to the acid compounds of formula I.

The preferred mode of administration is oral. The compositions used may be in the form of solid, semi-solid or liquid dosage forms, such as, for example, tablets, pills, capsules, powders, liquids, suspensions, preferably in unit dosage forms suitable for single administration of precise dosages. The compositions will include a conventional pharmaceutical carrier or excipient and an active compound of Formula I, II and III or the pharmaceutically acceptable salts thereof and, in addition, may include other medicinal agents, pharmaceutical agents, carriers, adjuvants, etc.

For solid compositions, conventional non-toxic solid carriers include, for example, pharmaceutical grades of mannitol, lactose, starch, magnesium stearate, sodium saccharin, talcum, cellulose, glucose, sucrose, and magnesium carbonate may be used. Liquid pharmaceutically administerable compositions can, for example, be prepared by dissolving, dispersing, etc. an active compound as defined above and optional pharmaceutical adjuvants in a carrier, such as, for example, water, saline, aqueous dextrose, glycerol, ethanol, and the like, to thereby form a solution or suspension. If desired, the pharmaceutical composition to be administered may also contain minor amounts of non-toxic auxiliary substances such as wetting or emulsifying agents, pH buffering agents and the like, for example, sodium acetate, sorbitan monolaurate, triethanolamine sodium acetate, triethanolamine oleate, etc. Actual methods of preparing such dosage forms are known, or will be apparent, to those skilled in this art; for example, see Remington's Pharmaceutical Sciences, Mack Publishing Company, Easton, Pa., 15th Edition, 1975. The composition or formulation to be administered will, in any

event, contain a quantity of the active compound(s) in an amount effective to alleviate the symptoms of the subject being treated.

For oral administration, a pharmaceutically acceptable non-toxic composition is formed by the incorporation of any of the normally employed excipients, such as pharmaceutical grades of mannitol, lactose, starch, magnesium stearate, sodium saccharin, talcum, cellulose, glucose, sucrose, and magnesium carbonate. Such compositions take the form of solutions, suspensions, tablets, pills, capsules and powders, sustained release formulations and the like. Such compositions may contain 1%-95% active ingredient, preferably 25-70%.

A preferred tablet formulation of compound of formula I is the enteric coated (EC) 500 mg tablet. An enteric coating is intended to prevent the active ingredients in the dosage form, from disintegrating in the stomach. The tablet will pass intact through the stomach to dissolve in the intestines (pH 5.7 to 7.4).

A wet granulation process prepares the tablet core. The following is an illustrative example of the composition of a typical 500 mg tablet.

Raw Material	% w/w	Amount per tablet (mg)
Compound of Formula I	93.8	500.00
Povidone (K-90)	2.0	10.66
Croscarmellose Sodium	4.0	21.32
Magnesium Stearate	0.2	1.07
	100.0	533.05
Purified Water	26.0	138.59

The tablet core contains a compound of formula I which is the bulk of the tablet. Magnesium stearate is used as the lubricant, povidone K-90 as a binder and croscarmellose sodium as a binder and disintegrant. Tablet

batches are typically coated to a tablet weight gain of 9 to 15%, with the following coating dispersion.

Raw Material	% w/w
Methacrylic Acid Copolymer, Type C (Eudragit L-100-55)	14.60
Talc	3.70
Sodium Hydroxide	0.20
Triethyl Citrate	1.50
Purified Water	80.00
	100.00

Eudragit L-100-55 contains the enteric polymer. Talc is used to prevent tablets from sticking together during the coating process. Sodium hydroxide pellets is used to obtain a dispersion of the enteric polymer and triethyl citrate is used as a plasticizer. The key features of the tablet core formulation include low excipient levels, no organic solvent in the granulation and good tablet core characteristics.

The amount of active compound administered depends on the subject being treated, the manner of administration and the judgment of the prescribing physician. However, an effective dosage is in the range of 1-100 mg/kg/day, preferably about 25 mg/kg/day. For an average 70 kg human, this would amount to 70 mg-7 g per day, or preferably about 1.5 g/day.

The following specific examples are provided as a general guide to assist the practice of this invention, and are not intended as a limitation on the scope of the invention.

Example 1

Preparation of 3-(benzyloxy)-1,6-dimethyl-4-oxo-1, 4-dihydropyridine-2-carboxylic acid.

2 M Methylamine solution in Methanol (5.8 ml, 11.5 mmol) was added to a suspension of the 3-(benzyloxy)-6-methyl-4-oxo-4H-pyran-2-carboxylic acid (1.0 g, 3.84 mmol) in Methanol (3 ml) at room temperature. The resulting solution was sealed, and then heated at 70 °C for overnight. A clear yellow solution was observed. The titled compound was obtained as a light yellow solid after solvent was removed by reducing pressure. The yellow solid was directly used for the next step reaction without further purification. (1.74 g, yield 97%). ^{1}H NMR (D MSO) σ: 7.70 (br, 1H,), 7.49 (m, 2H), 7.30 (M, 3H), 6.01 (S, 1H), 4.90 (s, 3H, CH_2), 3.47 (S, 3H, NMe), 2.2 (S, 3H, CH_3), MS: 274 (M + 1).

Example 2

Preparation of 3-hydroxy-1, 6-dimethyl-4-oxo-1, 4-dihydropyridine-2-carboxylic acid.

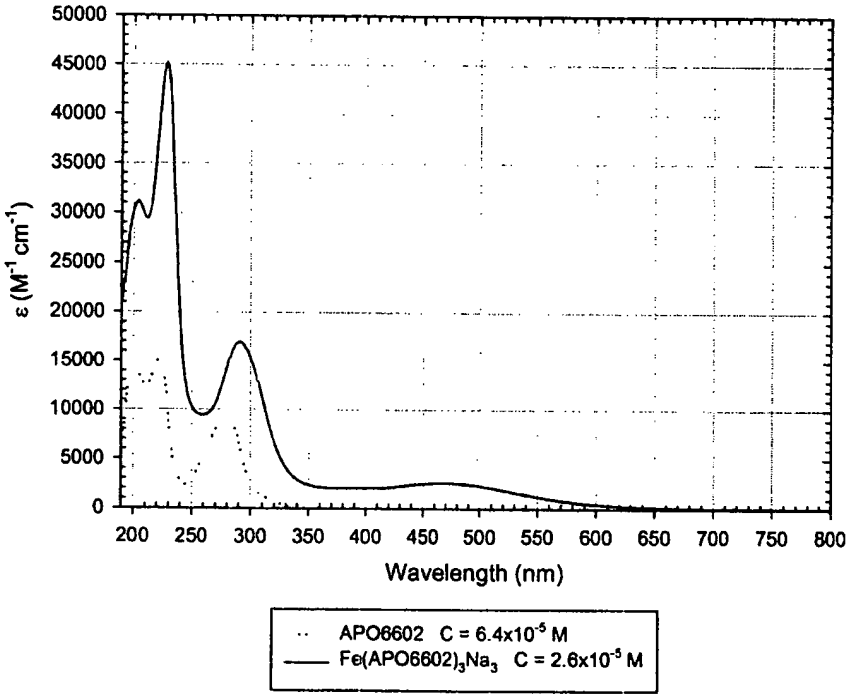
A solution of 3-(benzyloxy)-1,6-dimethyl-4-oxo-1, 4-dihydropyridine-2-carboxylic acid (5.0 g, mmol) in 200 ml of ethanol was hydrogenated under 50 Psi in presence of 10% Pd/C (0.35 g) at room temperature for 5 hours. The Palladium catalyst was removed by filtration via a layer of celite. The filtrate was collected, and concentrated to give slightly pink solid, which was purified by recrystallization from methanol to give the titled compound as white solid. (2.6 g, yield 78%), ^{1}H NMR (DMSO) σ: 7.85 (br, 1H), 6.02 (S, 1H), 3.82 (S, 3H, NMe), 2.26 (S, 3H, CH_3), MS: 184 (M + 1).

Example 3

Preparation of iron complex chelate from a compound of Formula I and a ferric salt.

NaOH (1.14 ml, 2N, 2.28 mmole) was added to a round bottom flask (25 ml). 3-hydroxy-1,6-dimethyl-4-oxo-1,4-dihydropyridine-2-carboxylic acid (210 mg, 1.147 mmole) was added in one portion. The mixture was stirred for five minutes. Ferric chloride hexahydrate ($FeCl_3.6H_2O$, 103.2 mg, 0.382 mmol)

was added. A reddish solution was formed. The mixture was stirred at room temperature for 60 hours at which time acetonitrile (20 ml) was added. The mixture was evaporated under reduced pressure to give an red oil. Ethanol (2 ml) was added and the material was evaporated to dryness under reduced pressure to afford a red solid. The red residue was dissolved in methanol (3 ml), and acetonitrile (10 ml) was added slowly. A red solid slowly appeared and the mixture was cooled in ice for 1.5 hr. The insoluble solid was filtered and dried to constant weight (250 mg). The UV spectrum is recorded in Tris buffer 7.4.

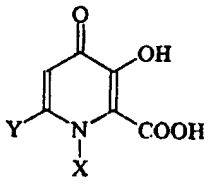


UV-Visible spectrum of ligand APO6602 (3-hydroxy-1,6-dimethyl-4-oxo-1,4-dihydropyridine-2-carboxylic acid) and $Fe(APO6602)_3Na_3$.

Mass spect.: 691 (M + Na), 647 (M + Na – CO_2), 603, 580, 555, 471, 393.

Claims

1. A compound of formula I or its pharmaceutically acceptable salt:



Formula I

wherein:

X is C_1-C_6 alkyl, C_3-C_6 cycloalkyl, and a C_1-C_6 alkyl substituted by a hydroxy group or a carboxylic acid ester, $CONH_2$, SO_2NH_2, sulfo acid ester, C_1-C_6 alkyoxy, benzyloxy or C_6-aryloxy ether thereof,
Y is hydrogen, C_1-C_6 alkyl, CH_2OR', $CH_2NR'R''$, CO-NHR' wherein R', R" are independently hydrogen, C_1-C_6 alkyl.

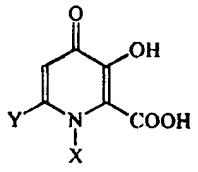
2. A compound of claim 1 wherein:
X is C_1-C_6 alkyl,
Y is C_1-C_6 alkyl.

3. A compound of claim 2 wherein:
X is methyl,
Y is methyl.

4. A compound of claim 3, the compound is 3-hydroxy-1,6-dimethyl-4-oxo-1,4-dihydropyridine-2-carboxylic acid.

5. A method in using an effective amount of compound of formula I and its pharmacuetically acceptable salt as a ligand L to remove iron via the formation of a water soluble iron complex chelate FeL_3Na_3.

6. A process for the preparation of compound of formula I:



Formula I

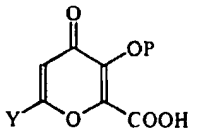
wherein:

X is C_1-C_6 alkyl, C_3-C_6 cycloalkyl,

Y is hydrogen, C_1-C_6 alkyl, CH_2OR', $CH_2NR'R''$, CO-NHR' wherein R', R" are independently hydrogen, C_1-C_6 alkyl;

which comprises of the following steps:

(a) reacting a compound of formula II:

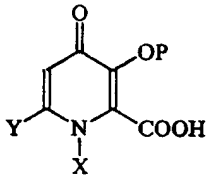


Formula II

wherein:

Y is hydrogen, C_1-C_6 alkyl, CH_2OR', $CH_2NR'R''$, CO-NHR' wherein R', R" are independently hydrogen, C_1-C_6 alkyl;

P is an alcohol protective group with an alkylamine XNH_2 wherein X is C_1-C_6 alkyl, C_3-C_6 cycloalkyl to give a compound of formula III:



Formula III

wherein Y, P and X are as defined above;

(b) deprotecting the C3 position alcohol protective group of a compound of a formula III from step (a) to give a compound of formula I.

7. A pharmaceutical composition comprising the compound of formula I or its pharmaceutical salt according to any one of claims 1 to 4 in admixture with a pharmaceutically acceptable diluent or carrier.

8. Use of a compound of any one of claims 1 to 4, for the treatment of beta-thalassemia.

9. Use of a compound of any one of claims 1 to 4, for the treatment of toxic concentration of iron in the body.